Central Neuropathic Pain

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REVIEW ARTICLE

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ABSTRACT

OBJECTIVE: **This article provides an approach to the assessment, diagnosis, and treatment of central neuropathic pain.**

LATEST DEVELOPMENTS: **Recent studies of the pathophysiology of central neuropathic pain, including evidence of changes in the expression of voltage-gated sodium channels and *N*-methyl-D-aspartate (NMDA) receptors, may provide the basis for new therapies. Other areas of current research include the role of cannabinoid-receptor activity and microglial cell activation in various animal models of central neuropathic pain. New observations regarding changes in primary afferent neuronal activity in central neuropathic pain and the preliminary observation that peripheral nerve blocks may relieve pain due to central neuropathic etiologies provide new insights into both the mechanism and treatment of central neuropathic pain.**

ESSENTIAL POINTS: **In the patient populations treated by neurologists, central neuropathic pain develops most frequently following spinal cord injury, multiple sclerosis, or stroke. A multimodal, individualized approach to the management of central neuropathic pain is necessary to optimize pain relief and may require multiple treatment trials to achieve the best outcome.**

INTRODUCTION

The International Association for the Study of Pain has defined central neuropathic pain as "pain caused by a lesion or disease of the central somatosensory system."[1] Central neuropathic pain can therefore be associated with a lesion involving the spinal cord, the brain, or both. Commonly cited examples of central neuropathic pain include central pain associated with spinal cord injury, central pain associated with multiple sclerosis (MS), and central poststroke pain; however, it is important to recognize that these are not homogeneous conditions. For example, spinal cord injury has multiple etiologies and can be associated with tumors, injury, infarction, inflammation, syringomyelia, and trauma. The presentation of central pain associated with MS may vary considerably between people, and central poststroke pain occurs as the result of a variety of cerebrovascular events.[2] In addition, central neuropathic pain has been described as a consequence of brain trauma or brain tumors as well as in individuals with Parkinson disease. This article focuses on the assessment and treatment of central neuropathic pain associated with spinal cord injury, central poststroke pain, and MS since these are the most common conditions associated with central neuropathic pain. Three cases exemplifying these conditions highlight the complexity of managing a person with any of these conditions.

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RELATIONSHIP DISCLOSURE:
Dr Argoff has received personal compensation in the range of $500 to $4999 for serving as a consultant for Nevro Corp, Scilex Holding, and Vertex Pharmaceuticals Incorporated and on a speakers bureau and as an expert witness for Scilex Holding; in the range of $5000 to $9999 for serving as a consultant for Collegium Pharmaceutical and Xgene Pharmaceutical Group, on a scientific advisory or data safety monitoring board for Vertex Pharmaceuticals Incorporated, and on a speakers bureau for Lundbeck; and in the range of $10,000 to $49,999 for serving on a speakers bureau for AbbVie, Inc. Dr Argoff has received publishing royalties from a publication relating to health care. The institution of Dr Argoff has received research support from AbbVie, Inc, Lilly, Lundbeck, and Vertex Pharmaceuticals Incorporated.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Argoff discusses several therapies, none of which are approved by the US Food and Drug Administration (FDA) for the treatment of central neuropathic pain.

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PATHOPHYSIOLOGY

The pathophysiology of central neuropathic pain is incompletely understood; however, several proposed mechanisms have emerged. Denervation hypersensitivity of remaining spinothalamic neurons following central nervous system (CNS) injury is one of the mechanisms that may lead to neuronal hyperexcitability in the CNS. A consequence of this process is that the threshold for action potential generation and propagation is decreased and there may be increased spontaneous and postdischarge responses to both non-noxious and noxious stimuli.[3] Abnormal spinothalamic tract function appears to be a nearly universal requirement in the emergence of central neuropathic pain. Since non-neuropathic pain conditions can develop in a person with a spinal cord injury, central poststroke pain, or MS, a person with a possible central neuropathic pain condition should be examined to determine if pain or temperature sensation is impaired in the affected limbs or body region. Noncentral neuropathic pain etiologies should be considered if pinprick and temperature sensation are normal.[4]

Changes in voltage-gated sodium channel expression patterns have been demonstrated in CNS neurons in rodent models of CNS injury. In a rodent model of spinal cord injury neuropathic pain, increased expression of $Na_V1.3$ was noted in the dorsal horn of the spinal cord and the thalamus, and increased expression of $Na_V1.5$ has been noted in MS demyelinating lesions.[3,5-7] The up-regulation of *N*-methyl-D-aspartate (NMDA)-receptor expression has been demonstrated in both a model of spinal cord injury and a model of central poststroke pain, perhaps providing the basis for why ketamine, an NMDA-receptor antagonist, has been shown to reduce both continuous and evoked spinal cord injury–related pain.[3,8] Several other classes of receptors have also been implicated in the pathophysiology of central neuropathic pain, including the calcium channel $\alpha_2\delta$ subunit in the dorsal horn of rats and the CB1 and CB2 cannabinoid receptors in models of spinal cord injury and cerebral ischemia.[3] These findings have potential clinical relevance given the availability of pharmacologic agents directed toward sodium channels (local anesthetics and certain anticonvulsants), the availability of $\alpha_2\delta$-subunit antagonists (gabapentin and pregabalin), and the demonstration that MS-related neuropathic pain may be responsive to cannabinoid-directed therapies.[3]

CNS inflammatory and immune mediators are also under active investigation for their role in the development of central neuropathic pain with microglial cell activation, with the overexpression of purinergic P2X receptors being demonstrated in various animal models.[9-11] Data has emerged suggesting that CNS injury can result in changes in the cell bodies of the dorsal root ganglia, primary afferent neurons, and the central and peripheral terminals of peripheral neurons. In central poststroke pain, complete but temporary pain relief was observed in 85% of patients with central poststroke pain who had been treated with an ultrasound-guided peripheral nerve block in the affected extremity. This observation is fascinating as it suggests that perhaps the central neuropathic pain associated with central poststroke pain is not completely caused by CNS activity but also requires input from primary afferents within the painful area. Although there is currently only one published case report to support the use of this modality, a separate published report describing the benefit of dorsal root ganglia stimulation in reducing central poststroke pain highlights an exciting observation and suggests the need for further study to better appreciate the respective roles of both peripheral and central mechanisms in central

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neuropathic pain.[12,13] Given the dearth of studies supporting a consistently effective approach to managing central neuropathic pain, the development of new safe and effective treatments would be most welcome.

DIAGNOSING CENTRAL NEUROPATHIC PAIN

This section describes approaches to diagnosing a central neuropathic pain condition. Distinguishing between central neuropathic pain states and non-neuropathic pain is important, especially when considering potential treatments.

Spinal Cord Injury Pain

Recent data suggests that the average patient age at the time of spinal cord injury has increased from approximately 29 years in the 1970s to 43 years in 2015. Motor vehicle accidents, falls, and injury due to violence or sports are the four most common causes of spinal cord injury, with motor vehicle accidents and falls totaling approximately 70% of cases.[3] Not all spinal cord injury–related pain is neuropathic and multiple nociceptive pain conditions have been described following spinal cord injury. Neuropathic pain associated with spinal cord injury is spontaneous and associated with hyperalgesia, and descriptors used to describe this pain include squeezing, burning, and shooting, with a prevalence according to one meta-analysis of 53%.[14,15] Non-neuropathic pain conditions experienced by patients following spinal cord injury include musculoskeletal pain, visceral pain, pain secondary to overuse, and pain associated with autonomic dysreflexia (including headache).[16] Perhaps not surprisingly, it may be difficult to attribute a pain symptom to a specific pain type, and the pooled prevalence of all types of spinal cord injury–related pain is estimated to be 80%.[17] Neuropathic pain occurring below the level of the spinal cord injury is classified as central; however, if neuropathic pain occurs at the level of the spinal cord injury it may be considered peripheral or central. For example, it is considered peripheral if the pain is caused by a lesion of the dorsal root and central if the pain is caused by a lesion of the dorsal horn. If pain is perceived within three levels below the injury, it is considered *at-level* pain, but if it is perceived greater than three levels below the lesion, it is considered *below-level* pain.[16] These pain levels can certainly overlap. Below-level pain tends to occur later than at-level pain and it has been observed to be more resistant to treatment.[17] Neuropathic pain associated with spinal cord injury does not generally improve over time; in fact, it is likely to worsen over time.[18]

Establishing the diagnosis of neuropathic pain, whether central or peripheral, is not always straightforward. Descriptions of symptoms may include terms such as tingling, burning, shocklike, pins and needles, tightness, squeezing, electric, cold, lancinating, and prickling. When evaluating a person with suspected neuropathic pain, the examiner may choose to use one of several validated diagnostic approaches. Multiple questionnaires have been developed to screen for neuropathic pain, including the Leeds Assessment of Neuropathic Symptoms and Signs, the painDETECT questionnaire, the Neuropathic Pain Questionnaire, and the Douleur Neuropathique 4.[19–22] In addition to these questionnaires, certain clinical signs are observable in patients experiencing neuropathic pain, including allodynia and hyperalgesia. Allodynia refers to pain occurring following a stimulus that is normally not painful, and hyperalgesia is the term used to describe the experience of increased pain from a stimulus that is normally painful.[3] The presence of these signs can be assessed during the neurologic

KEY POINTS

- The development of central neuropathic pain may occur following an injury of or in association with a disorder affecting the spinal cord or brain.
- Abnormal spinothalamic tract function is nearly always present in a person experiencing central neuropathic pain.
- Non-neuropathic pain may exist concurrently in a person experiencing central neuropathic pain.
- Mechanisms underlying central neuropathic pain include those involving both the peripheral and central nervous systems.
- Approximately 70% of spinal cord injuries are associated with a motor vehicle accident or a fall.
- Central neuropathic pain associated with spinal cord injury may occur concurrently with non-neuropathic pain associated with spinal cord injury, emphasizing the need for a formal neurologic assessment.

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examination, emphasizing the importance of a formal assessment for these findings (CASE 4-1).

Central Poststroke Pain

Central poststroke pain is the most common form of central neuropathic pain.[4] In general, pain after a stroke is highly prevalent and, in addition to central poststroke pain, can present as musculoskeletal symptoms, headache, or spasticity. An important risk factor for central poststroke pain is stroke location. Thalamic strokes (Dejerine-Roussy syndrome) and lateral medullary strokes (Wallenberg syndrome) are associated with the highest incidence of central poststroke pain. Thalamic strokes are associated with between 25% and 33% of instances of central poststroke pain. Within the thalamus, the risk of central poststroke pain is higher when the ventral posterior nucleus is involved and lower when the centromedian or median nuclei are affected.[23-25] The development of central poststroke pain is associated with lesions involving the spinothalamic tracts terminating within the ventral posterolateral thalamus and lesions of the mesial lemniscal pathway and ventral posteromedial thalamus.[26] Lateral medullary strokes are associated with disturbed pain and temperature sensation on the ipsilateral face and contralateral body, facial numbness, ptosis, and contralateral spinothalamic sensory loss.[27] Strokes involving the

CASE 4-1

A 44-year-old man experienced a spinal cord injury 5 years ago following a ruptured arteriovenous malformation at the C3 level, resulting in spastic quadriparesis. Within the following year, he experienced severe dysesthesia in his lower extremities and burning pain in his trunk below his nipple line. These occurred independent of the pain associated with his spasticity and muscle spasms. In addition, he reported bilateral shoulder, hip, and low back pain. Multiple specialist evaluations included physiatry, orthopedics, neurology, neurosurgery, and pain management. He was hospitalized multiple times for symptomatic treatment and inpatient rehabilitation.

On neurologic examination, manual muscle testing revealed symmetric 4-/5 weakness in the deltoid, biceps, triceps, wrist extensor, and intrinsic hand muscles. Hip flexors, quadriceps, hamstrings, and tibialis anterior muscles demonstrated symmetric 2/5 weakness. Muscle stretch reflex testing revealed hyperreflexia with sustained bilateral ankle clonus and bilateral extensor plantar responses. Sensory examination was inconsistent, with variable responses to light touch, pinprick, vibratory, and position sense testing. There was notable hyperalgesia and allodynia over the lower anterior chest wall and both upper extremities in a nondermatomal pattern.

Before his pain management evaluation, treatment included trials of oral baclofen 80 mg/day, tizanidine 24 mg/day, and onabotulinumtoxinA injections for his spasticity, with suboptimal responses. Additional treatments included gabapentin up to 3600 mg/day, pregabalin up to 600 mg/day, amitriptyline up to 100 mg/day, carbamazepine 500 mg/day, duloxetine 60 mg/day, lacosamide 400 mg/day, buprenorphine buccal

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dorsal basal ganglia, posterior internal capsule, putamen, and parietal cortex may also result in central poststroke pain.[28,29] The risk of central poststroke pain is similar whether the stroke is ischemic or hemorrhagic.[4] Central poststroke pain usually occurs within 3 to 6 months of the stroke and is associated with altered temperature thresholds, allodynia, and hyperesthesia.[23] The neurologic examination of a person with suspected central poststroke pain must therefore include a general neurologic examination and a sensory examination that can assess for the findings noted above (CASE 4-2).

Multiple Sclerosis–related Pain

MS is an autoimmune disorder associated with demyelinating plaques within the brain and spinal cord. MS can be associated with multiple forms, including a progressive form and the more commonly experienced relapsing-remitting course with the onset of neurologic impairment followed by improvement and periods of stability. With either form, as the disease progresses, chronic pain may occur in as many as 80% of patients.[30] MS-associated trigeminal neuralgia is the presenting symptom of MS in 14% of patients.[31] A characteristic sign associated with MS is the Lhermitte sign, in which neck flexion results in the sudden onset of an electrical shooting sensation traveling from the neck down to other areas of the spine and sometimes into the lower extremities. This sign has

film 1.5 mg/day, milnacipran 100 mg/day, mexiletine, IV lidocaine infusions up to a dose of 4 mg/kg/hour for 4 hours/session weekly for 4 weeks, and tramadol, without significant improvement. Routine laboratory testing including serum vitamin B_{12} level was unremarkable.

The patient was advised of the potential for the use of intrathecal approaches to spasticity and pain management. After a successful test dose of intrathecal baclofen was completed, he underwent implantation of an intrathecal pump system and his spasticity control improved dramatically; however, his lower extremity dysesthesia and burning pain did not. He was offered multiple options, including retrialing an oral medication he had used before the pump implantation or considering the addition of ziconotide to his pump. After a test dose of intrathecal ziconotide was successfully completed, he noted significant improvement in the lower extremity dysesthesia and burning pain, and he continued to receive a combination of intrathecal baclofen 600 µg/day and ziconotide 2.4 µg/day.

COMMENT

Below level of injury pain following spinal cord injury can occur years after the injury. This is considered a central neuropathic pain type and it can be challenging to treat. It is important to recognize that concurrent pain types that may be experienced by a person following spinal cord injury include chronic musculoskeletal pain, neuropathic pain unrelated to the spinal cord injury, peripheral neuropathic pain related to the spinal cord injury, and other nonspinal cord injury–related pain syndromes.

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CASE 4-2

A 48-year-old man presented to the clinic for evaluation of facial and left upper and lower limb pain. His history was notable for a right lateral medullary ischemic infarction at age 33 years. Within several months following the stroke, he began to experience bilateral facial pain and burning pain over his left trunk and upper and lower extremities. His examination in the clinic demonstrated residual deficits from the stroke, including decreased sensation to light touch and pinprick and temperature sensation over the left trunk and upper and lower extremities. He was mildly unsteady and ambulated with a cane.

Prior trials of gabapentin, duloxetine, amitriptyline, and pregabalin were unsuccessful. He underwent trials of carbamazepine, oxcarbazepine, and lamotrigine, also without benefit. A trial of IV lidocaine infusions dampened the pain somewhat, but not to a clinically meaningful extent, so these were not continued. He was treated with physical therapy on multiple occasions and a trial of acupuncture was unsuccessful. He developed several other pain symptoms, including chronic migraine and chronic neck pain. He was found to have multilevel cervical facet arthropathy and he was treated successfully with topiramate and fremanezumab for his migraine. He was considered for cervical facet blocks and denervation, but he declined. Lacosamide was added to his regimen, followed by baclofen, with more success than with other pharmacologic approaches. The addition of extended-release oxycodone was also helpful. He was monitored regularly and settled into a pharmacologic analgesic regimen that included topiramate 100 mg/day, extended-release oxycodone 36 mg 2 times a day, lacosamide 200 mg 2 times a day, baclofen 20 mg each morning and 40 mg each evening, subcutaneous fremanezumab 225 mg/1.5 mL monthly, and ubrogepant 100 mg as needed at the onset of migraine. Although his pain was not completely controlled, he could function independently with a consistent 50% reduction in his central poststroke pain.

COMMENT

Although this patient experienced pain consistent with central poststroke pain, he also experienced other pain (eg, migraine, chronic neck pain) that may have had an onset after his stroke but would not be considered typical central poststroke pain. Furthermore, his migraine was responsive to acute and preventative pharmacotherapy. Few randomized controlled trials assessing the treatment of central poststroke pain have been completed, and there are no published multidrug studies of central poststroke pain. In addition, this patient was reluctant to undergo additional treatments that may have added to his pain relief. Therefore, the treatment of central poststroke pain in a practice setting is likely to be associated with multiple treatment trials and the use of a combination of pharmacologic and nonpharmacologic therapies.

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been reported in 7% to 41% of patients with MS.[32-34] Recent studies support that the Lhermitte sign is associated with abnormalities of posterior column function and not spinothalamic tract dysfunction.

Twelve to twenty-eight percent of patients with MS will experience central neuropathic pain during their lifetime. It often occurs more than 1 year after the onset of symptoms and can occur in more than one location at a time. This multifocality should not be surprising since demyelinating lesions occur in multiple locations.[4] Central neuropathic pain associated with MS may occur in areas associated with spinothalamic tract sensory loss and is more common in patients with a progressive MS course, greater disability, longer MS duration, and older age.[35-38] MS-related central neuropathic pain may occur in a patient with MS with spasticity; however, these may not always exist concurrently and therefore need to be considered separately (CASE 4-3).

Proposed Standardized Diagnostic Criteria

Diagnostic criteria for central neuropathic pain conditions were proposed in 2017 through the collaborative effort of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy initiative.[2] TABLE 4-1 lists the proposed diagnostic criteria for central neuropathic pain associated with spinal cord injury, central poststroke pain, and MS. For central neuropathic pain associated with spinal cord injury or central poststroke pain, it should be noted that the criterion that the pain onset is up to 1 year following the injury is in contrast to multiple reports of central neuropathic pain having an onset years after the injury.[4]

TREATING CENTRAL NEUROPATHIC PAIN

The management of central neuropathic pain is often challenging as there is a scarcity of large, high-quality randomized trials, and those that have been completed have often provided conflicting results. Staudt and colleagues[39] recently published the results of a prospective trial in the management of central neuropathic pain in which only 9.6% of patients achieved the primary outcome of 30% or greater reduction in pain intensity and a 1-point reduction on the Pain Interference Scale over a 12-month period. Pharmacologic therapies and to a lesser extent invasive pain management strategies comprise the majority of published evidence for the management of central neuropathic pain.

Antiseizure Medications

Gabapentin and pregabalin, sometimes referred to as gabapentinoids, are commonly prescribed for various neuropathic pain conditions such as painful diabetic neuropathy and postherpetic neuralgia. Although they share a common mechanism of action, their pharmacokinetics are different, with the bioavailability of pregabalin being much greater than that of gabapentin.[3] Multiple randomized controlled trials have demonstrated the potential benefit of pregabalin in the management of spinal cord injury–related pain in doses up to 600 mg/day compared with placebo.[40-42] There are mixed data for gabapentin use in spinal cord injury–related neuropathic pain and virtually no evidence for its use in MS-related neuropathic pain.[43,44] One observational study involving 84 patients with central poststroke pain following a thalamic stroke demonstrated that 59.5% of patients using gabapentin 600 mg/day for 1 month experienced clinically significant pain relief.[45] An open-label trial of pregabalin involving

KEY POINTS

- Central poststroke pain is the most common type of central neuropathic pain.
- Stroke location is an important risk factor for the development of central poststroke pain.
- Chronic pain occurs in the majority of patients diagnosed with multiple sclerosis (MS).
- Central neuropathic pain is one of several types of pain that a person with MS may experience, and formal assessment for each type of MS-related pain should be completed.
- MS-related central neuropathic pain is more likely to occur in patients with a progressive MS course, older age, greater disability, and longer MS duration.
- Formal diagnostic criteria for central neuropathic pain associated with spinal cord injury, MS, or central poststroke pain have been recently proposed.
- There is a scarcity of large, high-quality randomized trials for central neuropathic pain.

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103 patients with any type of central neuropathic pain demonstrated that a dose range of 150 mg/day to 600 mg/day provided sustained benefit over 53 weeks.[46] A 2022 study involving patients from Japan, Korea, and Taiwan evaluated the role of mirogabalin, an $\alpha_2\delta$ agonist not currently available in the United States, for central neuropathic pain after spinal cord injury; responder rates for 30% or greater and 50% or greater pain intensity reduction were higher for treated patients compared with placebo at 14 weeks.[47]

Additional antiseizure medications that have been evaluated for central neuropathic pain include lamotrigine, levetiracetam, lacosamide, valproic acid, phenytoin, and topiramate. A randomized controlled study evaluating lamotrigine in the management of central poststroke pain suggested that 200 mg/day may be effective, while an open-label study comparing lamotrigine to gabapentin in 30 patients with central poststroke pain demonstrated that 10 patients experienced more than 50% pain reduction when they were treated with lamotrigine.[48,49] Patients with central neuropathic pain due to spinal cord injury were treated with lamotrigine in a randomized, crossover trial in which doses of up to 400 mg/day were used, without any difference seen during the different treatment periods.[50]

CASE 4-3

A 66-year-old man had secondary progressive multiple sclerosis (MS), which he had managed for many years with an MS specialist. He had multiple pain symptoms, including spasms due to his lower and upper extremity spasticity, chronic bilateral shoulder pain, chronic low back pain, and left-sided trigeminal neuralgia. When he first presented to the pain management center for further treatment consideration, he was being treated with carbamazepine 600 mg 2 times daily, oral baclofen 20 mg 4 times daily, and lamotrigine 200 mg 2 times daily. This regimen provided him with some benefit, but he still experienced frequent paroxysms of burning, lancinating, and shocklike pain affecting the left V2 and V3 distributions. These paroxysms would last for days at a time, during which he was unable to eat, chew, brush his teeth, comb his hair, or have anything touch this part of his face without experiencing severe pain. He used a wheelchair and lived in a skilled nursing facility. Prior treatments for the trigeminal neuralgia had included gabapentin, nortriptyline, pregabalin, duloxetine, and as-needed use of either oxycodone or hydrocodone.

Brain MRI with and without contrast demonstrated sequelae of MS affecting both cerebral hemispheres and the brainstem. There was no evidence of new lesions, active enhancing demyelinating plaques, or vascular compression of the left trigeminal nerve. A neurosurgical consultation resulted in several recommendations, including a rhizotomy or gamma knife radiosurgery. A rhizotomy was performed but was not helpful, and the patient was ultimately not thought to be an appropriate candidate for gamma knife radiosurgery. His neurologic examination was most notable for severe allodynia and hyperesthesia over the left V2 and V3 distributions with multiple trigger zones in these regions including intraoral, as well as lower extremity spasticity, diffuse hyperreflexia, ankle clonus, and bilateral extensor plantar responses.

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Based on randomized controlled trial results, there is no evidence for the use of levetiracetam for spinal cord injury or central poststroke pain and conflicting results for its use in MS-related central neuropathic pain.[3] A single randomized controlled trial involving patients with spinal cord injury–related pain did not demonstrate any benefit of sodium valproate compared with placebo.[51] One case report described the benefit of topiramate in a patient with MS-related pain, and while there is evidence for the use of lacosamide in peripheral neuropathic pain, there are no human studies demonstrating its benefit in central neuropathic pain.[52,53] One study of the treatment of central poststroke pain with phenytoin showed that an equal number of patients experienced pain relief as did those who experienced increased pain with phenytoin use.[54]

Antidepressants

Although antidepressants have been extensively studied in the management of neuropathic pain, there are few studies involving central neuropathic pain. Currently, available data suggest that amitriptyline may have benefit in certain patients with central neuropathic pain.[55] Although it is often considered a

The patient was presented with several treatment options. He derived no benefit from IV lidocaine or medical cannabis but responded favorably to subcutaneously administered injections of onabotulinumtoxinA into the skin overlying the left V2 and V3 regions. This off-label use of onabotulinumtoxinA helped him consistently for several years. He no longer used oral opioids or oral antiseizure medications, and the subcutaneously administered onabotulinumtoxinA injections did not result in facial muscle paralysis or asymmetry.

COMMENT

This patient's trigeminal neuralgia symptoms appeared to have been related to demyelinating plaque affecting the trigeminal nerve root entry zone, as evidenced by his MRI findings. His imaging did not suggest that he was an appropriate candidate for microvascular decompressive surgery, which is important to consider as a person with MS may develop trigeminal neuralgia as a consequence of vascular compression of the trigeminal nerve, similar to a person who develops trigeminal neuralgia without MS, suggesting in that instance that decompressive surgery might be helpful. In this case, the patient's trigeminal neuralgia is an example of an MS-related central neuropathic pain condition that developed as a consequence of demyelination. OnabotulinumtoxinA was used in this setting successfully and in an off-label manner, and there is evidence that onabotulinumtoxinA may be effective in reducing pain in other neuropathic pain states.

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treatment for MS-related pain, there is very little evidence to support its use.[56] Two studies involving the use of duloxetine in central neuropathic pain have been published. In an open-label study of central poststroke pain, duloxetine 30 mg/day to 60 mg/day was associated with a 48% decrease in pain intensity using the Numeric Pain Rating Scale after 3 weeks.[57] In a randomized controlled study of patients with either spinal cord injury–related pain or central poststroke pain, duloxetine 60 mg/day to 120 mg/day did not significantly decrease mean pain intensity, but there was an improvement in dynamic evoked pain and cold allodynia in the treatment group.[58] In contrast, two randomized controlled trials showed that duloxetine 30 mg/day to 60 mg/day was associated with significant pain reduction compared with placebo in patients with MS-related neuropathic pain.[59,60]

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TABLE 4-1 AAPT Diagnostic Criteria for Central Neuropathic Pain Conditions[a]

Spinal cord injury–associated pain

- Diagnostic test confirming spinal cord injury
- Continuous or recurrent pain after a spinal cord injury with onset of pain at the time of or up to 1 year after the spinal cord injury
- Pain duration of at least 3 months
- Pain is located in the area of the body associated with the spinal cord injury
- Pain is associated with sensory changes in a neuroanatomically plausible distribution
- No other diagnosis more appropriately explains the pain

Central poststroke pain–associated pain

- Diagnostic test or history confirming or strongly suggestive of a stroke
- Continuous or ongoing pain after a stroke whose onset is at the time of the stroke or up to 1 year after stroke onset
- Pain duration of at least 3 months
- Pain is located within the body area affected by the stroke
- Pain is located within a neuroanatomically plausible distribution
- No other diagnosis more accurately explains the pain

MS-associated pain

- Established MS
- Continuous or recurrent pain after the established diagnosis of MS
- Pain duration of at least 3 months
- Pain is experienced within an area of the body that would be affected by MS lesions within the brain or spinal cord
- Pain is located within a neuroanatomically plausible distribution
- No other diagnosis to explain the pain

AAPT = Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy; MS = multiple sclerosis.
[a] Data from Widerström-Noga E, et al, J Pain.[2]

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Local Anesthetics

Local anesthetics block sodium channels and these agents have been used intravenously, orally, and topically. One randomized, double-blind, crossover trial studied IV lidocaine administered at a dose of 5 mg/kg over 30 minutes in 16 patients with spinal cord injury–related pain or central poststroke pain. Ten patients reported a greater than 50% reduction in spontaneous pain for up to 1 hour following the infusion. Twelve of the 16 patients were placed on oral mexiletine, an oral local anesthetic agent, with doses titrated to 400 mg/day to 800 mg/day, but the side effects resulted in no patient wanting to continue this medication, and only three patients noted significant relief.[61] One crossover trial of patients with spinal cord injury–related pain and another trial of patients with MS-related pain demonstrated temporary improvement in pain intensity following IV lidocaine infusions.[62,63] A 2022 systematic review of the role of IV lidocaine in the management of chronic neuropathic pain including patients with spinal cord injury–related pain concluded that larger randomized, double-blind, placebo-controlled trials are needed as there is insufficient evidence to make a recommendation regarding this modality for this population.[64]

OnabotulinumtoxinA

Although the mechanism of action of onabotulinumtoxinA has been traditionally associated with the inhibition of acetylcholine release resulting in muscle relaxation, it has also been shown to inhibit the release of neurotransmitters and neuropeptides with "analgesic relevance," such as calcitonin gene–related peptide, substance P, and glutamate, as well as reduce the expression of receptors (P2X3 and TRPV1) relevant to pain and inflammation. This mechanism may be relevant to both central and peripheral neuropathic pain, in part because onabotulinumtoxinA has been shown to reach the CNS via retrograde transport. OnabotulinumtoxinA has been successfully used in patients with poststroke and MS-related spasticity, and published case reports and randomized controlled trial results describe the benefit of onabotulinumtoxinA when injected subcutaneously at the site of the worst pain in patients with spinal cord injury–related pain.[65-70]

Cannabinoids

Cannabinoids act on multiple targets within the endocannabinoid system, and those that have been evaluated in neuropathic pain conditions include delta-9-tetrahydrocannabinol, dronabinol, nabilone, inhaled cannabis, and nabiximols (derived from plant extracts with various concentrations of delta-9-tetrahydrocannabinol and cannabidiol).[71] The majority of studies regarding cannabinoids for central neuropathic pain have been in MS-related pain. A meta-analysis evaluating more than 3000 patients with MS concluded that there is a small therapeutic benefit for multiple MS-related symptoms including central neuropathic pain.[72] In contrast, a different systematic review of three studies of cannabinoids in the treatment of MS-related neuropathic pain concluded that there is no meaningful evidence to support their use for analgesic purposes for patients with MS-related neuropathic pain.[71]

Opioids

Opioids are complicated medications to consider in any chronic pain setting. For central poststroke pain, a meta-analysis concluded that there is no clear evidence

KEY POINTS

- Multiple antiseizure medications have been evaluated for different central neuropathic pain states with mixed results.
- Based upon the results of two randomized controlled trials, duloxetine may be considered for MS-related neuropathic pain.
- Small studies suggest the potential role of IV lidocaine infusions for the treatment of central neuropathic pain.
- In addition to its role in the treatment of spasticity, onabotulinumtoxinA has been demonstrated to reduce pain in patients with spinal cord injury–related neuropathic pain when injected subcutaneously.
- Insufficient evidence is currently available regarding the effect of cannabinoids on central neuropathic pain.
- Insufficient evidence is available to broadly recommend chronic opioid therapy for the management of central neuropathic pain.

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to support the efficacy of opioids in the management of poststroke pain.[73] Levorphanol was evaluated in 81 patients with resistant neuropathic pain, with five patients experiencing spinal cord injury–related pain and eight patients experiencing MS-related pain. Although both low-dose and high-dose levorphanol treatments resulted in pain reduction, 27% of patients did not complete the study due to side effects. In patients with spinal cord injury–related pain already being treated with antiseizure medications, the addition of oral oxycodone was associated with additional analgesic benefit.[74] Based on the available data, broad recommendations regarding the use of opioids for central neuropathic pain cannot be made.

Neuromodulation

A recent review of spinal stimulation for the treatment of peripheral or central neuropathic pain concluded that there is insufficient evidence to support its use in central neuropathic pain.[75] Intrathecal medications such as baclofen, morphine, or ziconotide have been used in the treatment of spasticity and chronic pain through an implanted catheter and pump. Intrathecal baclofen is used in the management of spasticity associated with stroke, cerebral palsy, MS, and spinal cord injury. Ziconotide is a conotoxin analog that blocks N-type voltage-gated calcium channels, and multiple randomized controlled trials have been published supporting its use for human immunodeficiency virus (HIV)-related pain, other noncancer-related pain, and cancer-related pain; however, no such study has been published for central neuropathic pain.[3] A 2009 case series suggested that intrathecal treatment with baclofen combined with ziconotide may help reduce both refractory neuropathic pain and spasticity.[76] Managing patients with implanted pumps requires a significant commitment given the need for ongoing monitoring, dose adjustments, refills, and monitoring for side effects.

Other Treatments

Nonpharmacologic treatments for central poststroke pain were evaluated in a 2020 systematic review, which concluded that some improvement was demonstrated with a range of therapies including transcranial direct current stimulation, bee venom acupuncture point injection, and caloric vestibular stimulation.[77] Transcranial magnetic stimulation when used over the primary motor cortex has been shown to be helpful in central poststroke pain.[78] A single case report described a reduction in lower extremity pain in a patient with a thalamic stroke through the use of dorsal root ganglia stimulation.[13] Of interest is that acupuncture, transcutaneous electrical nerve stimulation, cognitive behavioral therapy, and self-hypnosis were not shown to improve spinal cord injury–related neuropathic pain according to a Cochrane review.[79] The results of studies of either IV or oral ketamine in patients with central neuropathic pain due to either MS or spinal cord injury are mixed.[3]

Suggestions for first-line pharmacologic agents include tricyclic antidepressants, duloxetine, venlafaxine, pregabalin, and gabapentin.[80] While the evidence for their use for specific central neuropathic pain states is limited, the reader may benefit from viewing these as considerations as opposed to treatments with clearly established benefit.[80] While the focus of this article has been on central neuropathic pain, it is important to remember that other painful conditions, such as joint pain due to immobility or osteoarthritis or pain due to a

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decubitus ulcer, may coexist in a person with central neuropathic pain and these need to be addressed and evaluated appropriately.

CONCLUSION

The management of central neuropathic pain is challenging, in large part because safe and effective treatments have not been identified based upon currently completed clinical trials of patients with central poststroke pain, spinal cord injury, or MS. Nevertheless, multiple treatments are available for consideration for patients with central neuropathic pain according to the established principles of evidence-based medicine. While much attention has been given to the CNS, recent advances in the evaluation of the pathophysiology of central neuropathic pain and very preliminary published clinical data suggest that the peripheral nervous system may play a role both in the pathophysiology of central neuropathic pain and as a target for treatment. Such advances are exciting and will hopefully lead to medical and nonmedical treatments that are more helpful for people experiencing central neuropathic pain. Consistent with evidence-based medicine, clinicians treating patients with central neuropathic pain can approach each person in a multidisciplinary manner to integrate available treatments on an individualized basis in the best interest of that person according to the best available evidence. This approach truly epitomizes the art and science of clinical neurology.

KEY POINTS

- **Insufficient evidence is currently available to define the role of various neuromodulation approaches in the management of central neuropathic pain.**
- **Limited high-quality evidence exists for the treatment of central neuropathic pain, with the exception of pregabalin for spinal cord injury–related neuropathic pain. Commonly prescribed medications for central neuropathic pain do not have significant published evidence to support their use in general but may be considered on an individual basis.**
- **Nonpharmacologic treatments for central neuropathic pain may be considered in addition to or in place of pharmacologic therapies for people with central neuropathic pain.**

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